Please cancel claims 31 and 33 without prejudice.

Remarks

Applicant submits that in addition to the listing of references in the Specification an IDS listing the references on a PTO-1449 form and a copy of each of the references was properly submitted on May 10, 2001. Applicant requests that the initialed form indicating that each of the references listed has been considered be included with the next Office Action or the Notice of Allowance. An additional copy of the PTO-1449 form has been submitted herewith for the convenience of the Examiner.

New Figures 1A and 1B with lead lines for reference numbers and descriptions are submitted herewith, and new Figures 4 and 5 with each of the three different tables designated with a different figure number (*i.e.*, Figure 4A, 4B, 4C, 5A, 5B, 5C) are submitted herewith. A new figure containing the various features of the invention is also being prepared. As soon as the new figure becomes available, it will be submitted to the PTO.

Claims 1-54 are pending in the application. Claims 1-54 stand rejected. Claims 1-7, 15, 23, 32, 34, 35, 41, and 45 are amended as above. Claims 31 and 33 have been canceled. No new matter is added to the Specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. §112, second paragraph, as being indefinite.** Claims 1-54 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner maintains that the step of "providing a patient" in claim 1 is improper because it appears that the applicant is attempting to claim a human being. Applicant submits that this language is not improper and that "providing a patient" is only the first step in a method of treating a patient. This language would in no way suggest to one of ordinary skill in the art that

the applicant is claiming a human being. However, to further prosecution, Applicant has amended claims 1 and 2 to obviate this rejection.

In claim 3, Examiner says that the phrase "shear stress seen by the vascular endothelial cells of the patient" is indefinite because it is not clear how to see the shear stress and what is the structural element being used to see such stress. Applicant submits that to one of ordinary skill in the art this language would be clear and definite. Reversing the shear stress on the cells would involve reversing the flow of blood in the vasculature. This reversal could be determined using any method known in the art including, for example, Doppler ultrasound. Applicant, however, in order to further prosecution amended claim 3 to recite "shear stress to which the vascular endothelial cells of the patient are subjected." Applicant submits that the amended claim is definite as written and requests that the rejection be removed.

In claim 8, Examiner says that the phrase "sufficient to cause temporary collapse" is vague and indefinite because this conditions varies with different patients. Although it may be true that the conditions required to cause temporary collapse may vary with different patients, Applicant submits that the pressure needed to cause collapse could be determined by one of ordinary skill in the art with an apparatus such as a stethoscope and a blood pressure cuff. Applicant therefore requests that the rejection be removed.

In claim 13, Examiner says it is not clear what is meant by "timed with the cardiac cycle of the patient". Applicant submits that this is clear in light of the teachings of the Specification. For example, one might wish to time applying graded sequential compression during systole in order to augment the pumping action of the heart, or one might wish to time applying retrograde graded sequential compression during diastole in order to prevent the compression working against the heart. This timing could be performed based on EKG measurements. Applicant requests that this rejection be removed because one of ordinary skill in the art would find this clear.

Claim 15 has been amended to obviate the Examiner's rejection by reciting that NO is nitric oxide.

In claim 19, Examiner again suggests that the language "apparatus is attached to at least one extremity of the patient" is indefinite because it appears that the applicant is attempting to

claim human anatomy. Applicant is *not* trying to claim human anatomy and is only pointing out where on the patient's body the apparatus is attached. Applicant submits that this would be clear to one of ordinary skill in the art and requests that the rejection be removed.

Applicant has amended claim 23 to remove "may" and obviate the Examiner's rejection.

Claims 27-30 further describe the patient being treated using the inventive method. The Applicant is in no way trying to claim a human subject with peripheral vascular disease, cardiovascular disease, coronary artery disease, or diabetes. Since this would be clear to one of ordinary skill in this art reading the Specification and Claims, Applicant requests that the rejection be removed.

Claim 35 has been amended to obviate the Examiner's rejection. Applicant submits that the amended claim is clear as to the compression structure performing the graded sequential compression.

Applicant submits that the antecedent basis for "liquid" can be found in claim 35, from which claim 40 depends. Therefore, "liquid" does not lack an antecedent basis, and Applicant requests that the rejection be removed.

Claim 41 has been amended to obviate the Examiner's rejection because of lack of antecedent basis for "withdrawal of fluid." In claim 43, a negative pressure reservoir is any structure have a lower pressure than the compression structure so that when the reservoir and the compression structure are allowed to communicate fluid is withdrawn from the compression structure into the reservoir. One example of a negative pressure reservoir is a vacuum pump.

Claims 45 has been amended to obviate the Examiner's rejection with respect to the use of the trademark Velcro®.

The control means in claim 54 is used to control the tension in the flexible band of the claimed apparatus. Applicant submits that this would be clear to one of ordinary skill in the art since the claim recites "a control means for controlling the tension in the band and thus the band's resulting pressure on the body part." Applicant respectfully requests that the rejection be removed.

II. **Rejection under 35 U.S.C. §101.** Claims 3-7, 12, and 14-18 stand rejected under 35 U.S.C. § 101 as being inoperative and therefore lacking utility. Applicant submits that the invention is not inoperative and therefore has utility in inducing angiogenesis or inducing wound healing. As discussed in the Specification starting at page 2, line 4, the endothelium including endothelial cells and smooth muscle cells have been shown by several research groups to be sensitive to fluid dynamic shear stress, and as a result of such stress these cells have been found to release various pro-angiogenic factors. By subjecting the endothelium of a human patient to changes in shear stress using the claimed invention, one can induce angiogenesis *in vivo*. In further support of the utility and operability of the claimed invention, *in vitro* results from recent studies by the inventors investigating the effect of shear stress on the expression of angiogenesis factors, including VEGF, MCP-1, GM-CSF, Angl, and Tie2, are submitted herewith in Declaration form. These results show that when endothelial cells experience changes in shear stress, they respond by changing the expression of various angiogenic factors. For example, the expression of MCP-1 and Tie2 increased as a result of increased shear stress experienced by endothelial cells while VEGF and GM-CSF seem to show decreased expression upon increased levels of shear stress. The Specification in the Example beginning on page 18 shows by computer modeling that one can induce changes in the shear stress experienced by endothelial cells using external graded sequential compression. These changes in shear stress would likely induce angiogenesis *in vivo* through the stimulation of endothelial cells to secrete pro-angiogenic factors. Therefore, Applicant has shown that one of ordinary skill in the art can induce angiogenesis or wound healing using the inventive method with a reasonable expectation of success.

III. **Rejections under 35 U.S.C. § 102**. Claims 1, 9, 10, 13, 19-23, and 26 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Neeman *et al.* (U.S. Patent 5,014,681). Examiner submits that Neeman teaches a method of treating low blood flow comprising the steps of attaching a compression apparatus to a body part and applying graded sequential compression with a maximum pressure less than 200 mm Hg. Applicant disagrees because Neeman does not teach *graded* sequential compression, wherein the pressure applied at the distal region of the limb is greater than the pressure applied at a more proximal region (see page 7, lines 5-11, of the

Specification). In order to anticipate a claim, the reference must teach every element of the claim. MPEP § 2131. Neeman does not teach this "graded" limitation of the present claims; therefore, Neeman cannot anticipate the claimed invention. Applicant requests that the rejection be removed.

Claims 1, 9, 10, 12, 13, 19, 20, 23, 25, and 26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by McEwen *et al.* (U.S. Patent 5,843,007). Examiner states that McEwen teaches a device comprising a plurality of cuffs; however, McEwen does not teach graded sequential compression as claimed in the present Application. In fact, McEwen does not teach compression that is graded or sequential. Since McEwen does not teach certain limitations of the present claims, Applicant submits that rejection should be removed.

Claims 31-34 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Spielberg *et al.* (U.S. Patent 3,859,989). Applicant submits that this rejection is not proper since the Examiner has not clearly pointed out how the pending claims are anticipated by the cited art. Applicant respectfully requests that the Examiner provide a more detailed explanation of his rejection of the amended claims 31-34 or remove the rejection.

Claims 35-37, 39, 40, 44, 47, 49, and 51-54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zheng *et al.* (U.S. Patent 5,997,540). The Examiner states that Zheng teaches a device having a plurality of balloons, a peak pressure of 60 mm Hg, a computer, a blood oxygen detector, pulse oximeter, blood pressure detector, cooling means, and mounting means. Although Zheng may teach a device having all these components, Zheng does not teach a device including a control means that provides graded sequential compression as recited in the pending claims. Since Zheng does not teach such a device that can provide graded sequential compression, Zheng cannot anticipate the claimed invention. Applicant, therefore, requests that the rejection be removed.

Claim 33 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Khouri (U.S. Patent 5,701,917). Claim 33 has been canceled obviating this rejection.

IV. **Rejections under 35 U.S.C. § 103**. Claims 2-8, 11, 12, 14-18, and 27-30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Neeman *et al.* (U.S. Patent 5, 014,681). Examiner states in his reasons for levying this rejection that the feature of using the compression

method to treat patients with such diseases and the maximum delivery pressure are an obvious design preference. The Examiner also states that Neeman's device would be able to perform the recited function of the present claims. However, this is not true. The present claims recite graded sequential compression. As described above, Neeman does not teach *graded* sequential compression, and graded sequential compression could not be performed using Neeman's device. Neeman's device would not allow one to apply greater pressure at the distal region of the limb as compared to the proximal region. Therefore, without a teaching of *graded* sequential compression, Neeman cannot render obvious the claimed invention. Applicant requests that the rejection be removed.

Claim 13 stands rejected under 35 U.S.C. § 103 as being unpatentable over Neeman *et al.* (U.S. Patent 5,014,681) in view of Dillon (U.S. Patent 5,514,079). The Examiner uses Dillon to teach a pulse monitor having an EKG and a timer and concludes that it would have been obvious to one of ordinary skill in the art to provide Neeman's device with a pulse monitor as taught by Dillon in order to enhance the treatment effect. Although this may be true, Neeman and Dillon still do not teach graded sequential compression as described above. Since these references even when combined fail to teach or suggest this limitation of the present claims, they cannot render obvious the claimed invention. Therefore, Applicant requests that the rejection be removed.

Claims 1-12, 14-22, 24-30, 35, 41-46, 48, 50, and 52-54 stand rejected under 35 U.S.C. § 103 as being unpatentable over Cariapa *et al.* (U.S. Patent 5,437,610). Examiner states that Cariapa teaches a hydraulic system including sequentially compressible bladders. Examiner, however, states that Cariapa does not teach the delivery of a maximum pressure of less than 300, 250, 200, or 150 mm Hg. Examiner maintains that choosing such a feature would be an obvious design choice. Applicant disagrees. The maximum pressure limitation is not an obvious design choice because Cariapa and the Applicant have two different goals in mind. Cariapa is using the device for treating edema while the present invention is directed to a method and apparatus for inducing angiogenesis or wound healing. In order to induce angiogenesis or wound healing, the endothelial cells of the patient must experience a change in shear stress, which may result from a lower maximum pressure than that needed to treat edema. Cariapa, since he was treating edema, would need a pressure high enough to reduce edema and would not design his system to merely

induce a change in shear stress experienced by the endothelial cells of the patients. Therefore, one of ordinary skill in the art reading Cariapa would not be taught to search for a pressure which would induce angiogenesis or wound healing given the different goal of Cariapa. Without this teaching or suggestion regarding the maximum pressure, Cariapa cannot render the claimed invention obvious given its importance in inducing angiogenesis or wound healing.

Claim 38 stand rejected under 35 U.S.C. § 103 as being unpatentable over Cariapa *et al.* (U.S. Patent 5,437,610) in view of Dillon (U.S. Patent 5,514,079). The Examiner has cited Dillon for teaching an EKG so as to provide better control during treatment. However, as described above, Cariapa does not teach the maximum compression pressure recited in the present claims, and Dillon does not teach this limitation even when combined with Cariapa. Since the references even when combined do not teach this limitation in the present claims, Applicant submits that the combined references do not render the claimed invention obvious and requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Date: February 7, 2003

Certificate of Mailing

I certify that this correspondence is being deposited with the United State: Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 2023:

February 7, 2003 — Linda M. Amato
Date — Signature

Linda M. Amato
Typed or Printed Name of person signing certificate

Appendix A

Marked-up Paragraphs

On page 1, line 20:

--One of the best ways of alleviating the problems of low blood flow and decreased perfusion is through angiogenesis in order to create new blood vessels to feed the affected area of the body. Angiogenesis has been found to be important in many pathological conditions such as cancer and retinal neovascularization as well as in normal physiological states such as wound healing and development. Angiogenesis is a complex biological process involving many factors and cell types to produce new blood vessels. Many natural factors have been found to have angiogenic activity including platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, *etc.* Arterial and venous endothelial cells and smooth muscle cells have been found to be sensitive to fluid dynamic shear stress and mechanical strain and to release pro-angiogenic factors (*e.g.*, platelet-derived growth factors A and B, and basic fibroblast growth factor) in response to such stimuli (Davies "Mechanisms involved in endothelial responses to hemodynamic forces" *Atherosclerosis* 131:S15-S17, June 1997; Diamond *et al.* "Tissue plasminogen activator messenger RNA levels increase in cultured human endothelial cells exposed to laminar shear stress" *Journal of Cell Physiology* 143:364-371, 1990; Hseih *et al.* "Shear stress increases endothelial platelet-derived growth factor mRNA levels" *American Journal of Physiology* 260:H642-H646, 1991; Malek *et al.* "Fluid shear stress differentially modulates expression of genes encoding basic fibroblast growth factor and platelet-derived growth factor B chain in vascular endothelium" *Journal of Clinical Investigation* 92:2013-2021, 1993; Mason "The ins and outs of fibroblast growth factors" *Cell* 78(4):547-552, August 1994; Mitsumata *et al.* "Fluid shear stress stimulates platelet-derived growth factor expression in endothelial cells" *American Journal of Physiology* 265(1):H3-H8, July 1993; Sumpio "Hemodynamic forces and the biology of the endothelium: signal transduction pathways in endothelial cells subjected to physical forces in vitro" *Journal of Vascular Surgery* 13(5):744-746, May 1991; Ichioka *et al.* "Effects of shear stress on wound-healing angiogenesis in the rabbit ear chamber" *Journal of Surgical Research* 72:29-35, 1997;

each of which is incorporated herein by reference). Shear stress is also instrumental in the control of nitric oxide, endothelin-1, transforming growth [factor• $_1$] factor β_1, and a host of others, many of which may also contribute to angiogenesis.--

On page 5, line 5:

--In a preferred embodiment, the angiogenic factors produced by the vascular cells in response to the external compression include, but are not limited to, growth factors (*e.g.*, platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, transforming growth [factor• $_1$] factor β_1, *etc.*), cytokines, prostaglandins, leukotrienes, endothelin-1, and nitric oxide (NO). In a preferred embodiment, the cells responding to the change in hemodynamic factors and responsible for producing the angiogenic factors may be endothelial cells, muscle cells, fibroblasts, epithelial cells, or smooth muscle cells.--

Appendix B

Pending Claims

1. (Amended) A method for treating a disease characterized by low blood flow by inducing angiogenesis, the method comprising steps of:

attaching a compression apparatus to a body part of a patient suffering from a disease characterized by low blood flow; and

applying graded sequential compression to the body part of the patient using the compression apparatus, wherein the compression delivers a maximum pressure of less than 300 mm Hg.

2. (Amended) A method for promoting wound healing, the method comprising steps of:

attaching a compression apparatus to a body part of a patient with a wound; and

applying graded sequential compression to the body part of the patient using the compression apparatus, wherein the compression delivers a maximum pressure of less than 300 mm Hg.

3. (Amended) The method of claim 1 or 2 wherein the graded sequential compression results in a reverse in direction of shear stress to which the vascular endothelial cells of the patient are subjected.

4. (Amended) The method of claim 1 or 2 wherein the graded sequential compression causes a 100% increase in shear stress seen by the vascular endothelial cells of the patient.

5. (Amended) The method of claim 1 or 2 wherein the graded sequential compression causes a 50% increase in shear stress seen by the vascular endothelial cells of the patient.

6. (Amended) The method of claim 1 or 2 wherein the graded sequential compression causes a 200% increase in shear stress seen by the vascular endothelial cells of the patient.

7. (Amended) The method of claim 1 or 2 wherein the graded sequential compression causes a 400% increase in shear stress seen by the vascular endothelial cells of the patient.

8. The method of claim 1 or 2 wherein the graded sequential compression is sufficient to cause a temporary collapse of the large arteries of the body part to which the compression means is attached.

9. The method of claim 1 or 2 wherein the graded sequential compression delivers a maximum pressure of less than 250 mm Hg.

10. The method of claim 1 or 2 wherein the graded sequential compression delivers a maximum pressure of less than 200 mm Hg.

11. The method of claim 1 or 2 wherein the graded sequential compression delivers a maximum pressure of less than 150 mm Hg.

12. The method of claim 1 or 2 wherein the graded sequential compression results in retrograde flow in the arterial vasculature of the patient.

13. The method of claim 1 or 2 wherein the graded sequential compression is timed with the cardiac cycle of the patient.

14. The method of claim 1 or 2 wherein the graded sequential compression induces secretion of angiogenesis factors.

15. (Amended) The method of claim 1 or 2 wherein the graded sequential compression induces secretion of at least one molecule selected from the group consisting of platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-

derived growth factor, prostaglandins, nitric oxide (NO), leukotrienes, and cytokines.

16. The method of claim 1 or 2 wherein the graded sequential compression induces secretion of growth factors.

17. The method of claim 1 or 2 wherein the graded sequential compression induces secretion of angiogenesis factors by vascular endothelial cells.

18. The method of claim 1 or 2 wherein the graded sequential compression induces secretion of angiogenesis factors by cells selected from the groups consisting of muscle cells, fibroblasts, epithelial cells, and smooth muscle cells.

19. The method of claim 1 or 2 wherein the compression apparatus is attached to at least one extremity of the patient.

20. The method of claim 1 or 2 wherein the compression apparatus is attached to at least one leg of the patient.

21. The method of claim 1 or 2 wherein the compression apparatus is attached to at least one arm of the patient.

22. The method of claim 1 or 2 wherein the compression apparatus is an inflatable bladder.

23. (Amended) The method of claim 22 wherein the inflatable bladder contains a gas.

24. The method of claim 22 wherein the inflatable bladder contains a liquid.

25. The method of claim 1 or 2 wherein the compression apparatus is a series of cuffs containing at least one inflatable bladder.

26. The method of claim 1 or 2 wherein the compression apparatus is a flexible, stretchable band capable of being under variable tension.

27. The method of claim 1 or 2 wherein the patient has peripheral vascular disease.

28. The method of claim 1 or 2 wherein the patient has cardiovascular disease.

29. The method of claim 1 or 2 wherein the patient has coronary artery disease.

30. The method of claim 1 or 2 wherein the patient has diabetes.

31. A method for treating a disease characterized by low blood flow by inducing angiogenesis, the method comprising steps of:

providing a patient suffering from a disease characterized by low blood flow;

attaching an apparatus to a body part of the patient for delivering a negative pressure; and

applying negative pressure to the body part of the patient using the apparatus.

32. (Amended) A method for treating a disease characterized by low blood flow by inducing angiogenesis, the method comprising steps of:

attaching an apparatus for delivering negative and positive pressure to a body part of a patient suffering from a disease characterized by low blood flow;

applying negative pressure to the body part of the patient using the apparatus; and

applying graded sequential compression to the body part of the patient using the apparatus.

33. A method for promoting wound healing, the method comprising steps of:

providing a patient with a wound;

attaching an apparatus to a body part of the patient for delivering a negative pressure; and

applying negative pressure to the body part of the patient using the apparatus.

34. (Amended) A method for promoting wound healing, the method comprising steps of:

attaching an apparatus for delivering negative and positive pressure to a body part of a patient with a wound;

applying negative pressure to the body part of the patient using the apparatus.; and

applying graded sequential compression to the body part of the patient using the apparatus.

35. (Amended) An apparatus for compressing a part of a patient's body in order to induce angiogenesis or wound healing, the apparatus comprising:

a source of fluid;

a compression structure for receiving the fluid;

a control means for controlling the fluid to achieve inflation and deflation of the compression structure, wherein the control means institutes inflation of the compression structure so that graded sequential compression of the body part by the compression structure results with a maximum pressure of less than 300 mm Hg.

36. The apparatus of claim 35 wherein the apparatus further comprises a blood oxygen detector.

37. The apparatus of claim 35 wherein the apparatus further comprises a pulse oximeter.

38. The apparatus of claim 35 wherein the apparatus further comprises an EKG detector.

39. The apparatus of claim 35 wherein the apparatus further comprises a blood pressure detector.

40. The apparatus of claim 35 wherein the apparatus further comprises a means for heating or

cooling the liquid.

41. (Amended) The apparatus of claim 35 wherein the apparatus further comprises a means for accelerating withdrawal of fluid from the compression means.

42. The apparatus of claim 41 wherein the means for accelerating the withdrawal of fluid from the compression means comprises a vacuum pump.

43. The apparatus of claim 41 wherein the means for accelerating the withdrawal of fluid from the compression means comprises a negative pressure reservoir.

44. The apparatus of claim 35 wherein the compression structure comprises a means for mounting compression means on the body part.

45. (Amended) The apparatus of claim 44 wherein the means for mounting is hook and loop fasteners (Velcro®).

46. The apparatus of claim 44 wherein the means for mounting is selected from the group consisting of buttons, snaps, elastic bands, and zippers.

47. The apparatus of claim 35 wherein the fluid is a gas.

48. The apparatus of claim 35 wherein the fluid is a liquid.

49. The apparatus of claim 35 wherein the source of compressed fluid is a gas compressor.

50. The apparatus of claim 35 wherein the source of compressed fluid is a tank of pressurized gas.

51. The apparatus of claim 35 wherein the compression structure is a balloon.

52. The apparatus of claim 35 wherein the compression structure is a bladder.

53. The apparatus of claim 35 wherein the control means comprises a computer.

54. An apparatus for compressing a part of a patient's body in order to induce angiogenesis or wound healing, the apparatus comprising:

at least one flexible band;

a means for mounting said band on the body part;

a control means for controlling the tension in the band and thus the band's resulting pressure on the body part.